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Overview and Diagnostic Approach in Autoimmune Neurology

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs McKeon and Pittock discuss the unlabeled/investigational use of azathioprine, bortezomib, corticosteroids, cyclophosphamide, inebilizumab, intravenous immunoglobulin (IVIg), mycophenolate mofetil, plasma exchange, rituximab, and tocilizumab for the treatment of autoimmune neurologic disorders.

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ABSTRACT

OBJECTIVE: **The field of autoimmune neurology is rapidly evolving. This article reviews the epidemiology and pathophysiology as well as current approaches to clinical and paraclinical assessment, testing paradigms, and general principles of treatment.**

LATEST DEVELOPMENTS: **Improved recognition of autoimmune diagnoses among patients who have phenotypically diverse, subacute onset neurologic presentations is facilitated by disease-specific antibody biomarker discovery. These antibodies have varying associations with paraneoplastic causation (from no association to greater than 70% positive predictive value), immunotherapy responses, and outcomes. To simplify assessment in an increasingly complex discipline, neurologic phenotype-specific serum and CSF antibody evaluations are recommended. Clinical trials have led to the approval of monoclonal therapies for neuromyelitis optica spectrum disorder (NMOSD) and are underway for *N*-methyl-D-aspartate (NMDA) receptor and leucine-rich glioma inactivated protein 1 (LGI1) encephalitides.**

ESSENTIAL POINTS: **Autoimmune neurology is now a mainstream subspecialty, consisting of disorders with diverse presentations detectable using antibody testing of serum and CSF. Early and sustained immunotherapy (eg, corticosteroids, intravenous immunoglobulin [IVIg], plasma exchange) is recommended and may be supplemented by immune suppressants (eg, rituximab or cyclophosphamide) to sustain responses and optimize outcomes.**

INTRODUCTION

Autoimmune neurology is a subspecialty field dedicated to neurologic disorders occurring in the setting of aberrant immune responses against self, usually diagnosable through the detection of neural IgG antibody biomarkers. In general, these disorders are clinically recognizable by their subacute onset (ie, rapid onset with progression to significant clinical impairment within days to no more than 12 weeks). Any level of the neuroaxis may be affected. Phenotypes are diverse; some are distinctly autoimmune, and others mimic disorders with alternative etiologies. Supportive diagnostic paraclinical findings may be forthcoming from

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MRI of the neuraxis, neurophysiologic testing, CSF parameters, and disease-specific neural antibody biomarkers detected in serum, CSF, or both. Although autoimmune neurologic disorders are usually defined by antibody biomarkers, seronegative equivalents are often recognized. For example, limbic encephalitis has diverse antibody associations, but seronegative limbic encephalitis also occurs.[1] In contrast, although multiple sclerosis and neurosarcoidosis are neuroimmunologic inflammatory diseases, they have no antibody biomarkers (and thereby are not antigen specific), and thus they are not considered autoimmune neurologic disorders.

Beyond antibody diagnostics, findings supportive of an autoimmune basis for a disorder include the presence of non-neurologic autoimmune diseases in affected patients. This is particularly true for patients with aquaporin-4 (AQP4) antibody–positive neuromyelitis optica spectrum disorder (NMOSD) and glutamic acid decarboxylase 65 (GAD65) antibody–associated disorders.[2,3] Phenotypes accompanying antibodies may be restricted or diverse. For example, *N*-methyl-D-aspartate (NMDA) receptor antibody detected in CSF is accompanied only by encephalitis of varying degrees of severity. On the other hand, antineuronal nuclear antibody type 1 (ANNA-1 [also known as anti-Hu]) could present with one of several different phenotypes such as classic limbic encephalitis, a restricted form of limbic encephalitis that presents with seizures only, myelopathy, sensory neuronopathy, and other neuropathic phenotypes or a multifocal encephalomyeloneuropathy.[4] Some of these disorders are accompanied by an early-stage cancer (paraneoplastic cause), and some may respond to immunotherapy. Because these disorders can occur at any nervous system level, may mimic other disorders, and are potentially treatable, autoimmune causation is now on the differential diagnostic list for most clinical presentations of subacute onset. Similarly, given that autoimmune neurology is an etiologic specialty rather than a traditional neurologic phenotype-based discipline, a strong grounding in general neurology is required to accurately formulate autoimmune diagnoses and distinguish those disorders from other etiologies. The incidence of autoimmune neurologic disorders has increased over time, which is attributable to improved recognition.

KEY POINTS

- **Autoimmune neurology is a subspecialty focused on the evaluation and treatment of patients with diverse neurologic disorders, typically diagnosable by antibody testing.**
- **The incidence of autoimmune neurologic disorders has increased over time, which is attributable to improved recognition.**

EPIDEMIOLOGY AND RISK FACTORS

Epidemiology studies undertaken in the current era of sensitive and specific antibody biomarkers have led to improved recognition of the incidence and prevalence of autoimmune neurologic disorders. In Olmsted County, Minnesota, the incidence of autoimmune encephalitis increased over time from 0.4/100,000 person-years (1995-2005) to 1.2/100,000 person-years (2006-2015), comparable with the incidence of infectious encephalitis, and African American people were disproportionately affected.[5] Pacific Islander, Māori, or Asian background appears to be a risk factor for NMDA receptor encephalitis,[6] whereas leucine-rich glioma inactivated protein 1 (LGI1) encephalitis is found predominantly in White and Asian individuals.[7] The increase in the incidence of autoimmune encephalitis is attributable to increased detection of people who are antibody positive.[5] The incidence of paraneoplastic neurologic syndromes in Olmsted County, Minnesota increased over time from 0.4/100,000 person-years (1987-2002) to 0.8/100,000 person-years (2003-2018).[8] The prevalence was 5.4/100,000 people. The prevalence of AQP4-IgG–positive NMOSD among White individuals ranges from 0.5 to 3.2/100,000 people, with an incidence of less than

1/1 million person-years.[9,10] Among East Asian individuals, the prevalence is higher (3.5/100,000 people), and among Black individuals, the prevalence is higher than 10/100,000 people.[10] Optic neuritis associated with myelin oligodendrocyte glycoprotein (MOG) IgG is almost twice as common as optic neuritis related to AQP4 IgG in Olmsted County but with much better visual outcomes.[11]

Risk factors for autoimmunity include age, sex, ethnicity, and various genetic factors.[12] Age likely has a role in the timing of the emergence of many disorders. For example, NMDA receptor encephalitis typically arises in children and younger adults.[13] In contrast, LGI1 encephalitis usually arises in patients older than 60 years.[14] As is the case for many autoimmune diseases, the frequency is higher among women for NMDA receptor encephalitis (the male-to-female ratio is 1:4) and AQP4 IgG–positive NMOSD (1:8). Some exceptions in which men are disproportionately affected include LGI1 encephalitis and lung cancer–related paraneoplastic neurologic disorders. Genetic susceptibility to autoimmunity is observed in the personal and family histories of autoimmunity encountered in patients with some disorders, such as GAD65 autoimmunity. Human leukocyte antigen associations have been found for several disorders of the IgG4-dominant subclass, including those associated with LGI1, contactin-associated proteinlike 2 (CASPR2), Ig-like cell adhesion molecule 5 (IgLON5) and Kelch-like protein 11 (KLHL11) autoimmunity. A human leukocyte antigen association has not been found for other disorders, such as autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy. Certain neural antibody–positive disorders have been encountered in the setting of rare monogenic immune deficiency disorders (eg, LGI1 encephalitis in patients with *FOXP3* variations).[12]

Although environmental factors (eg, sun exposure and vitamin D levels) are known to modify the risk of multiple sclerosis, environmental factors have not been identified for autoimmune neurologic disorders. An epigenetic mechanism, or the regulation of gene expression by a specific profile of microRNA,[15] may be a factor in NMOSD. Tumor-expressed neural antigens and some viral antigens (eg, herpes simplex virus type 1 [HSV-1]) are implicated as triggers of loss of self-tolerance in paraneoplastic and parainfectious neurologic autoimmunity, respectively.[16] The pharmacologic blockade of immune checkpoints (programmed cell death 1, programmed death-ligand 1, cytotoxic T-lymphocyte antigen 4) in the treatment of cancer is also implicated in triggering paraneoplastic autoimmunity.[17] Risk factors that should be considered when evaluating autoimmune neurologic disorders include cancer history, smoking history, other autoimmune disease history, and immune checkpoint inhibitor use for cancer.[18] However, more often than not in clinical practice, initiating factors for autoimmunity are not discerned.

PATHOPHYSIOLOGY

Studies of paraneoplastic neurologic disorders and post-HSV-1 encephalitis have been informative of disease mechanisms. For paraneoplastic disorders, onconeural antigens expressed by tumors are released on tumor-cell death, processed, and presented by antigen-presenting cells to the T cells in regional lymph nodes. Presentation of an antigen complexed to major histocompatibility complex (MHC) class 1 results in the priming of $CD8^+$ cytotoxic T cells that migrate to both the cancer site and the nervous system to produce cytotoxic

effects. $CD4^+$ helper T cells are primed via the MHC class II pathway and activate antigen-specific B cells to differentiate into plasma cells and produce antibodies. The subcellular location of the antigen targeted during the autoimmune response, broadly speaking, represents two groups of biomarker antibodies: (1) those with intracellular antigens (T cell–mediated effectors) (FIGURE 1-1 and TABLE 1-1[19]) and (2) those with cell-surface plasma membrane antigens (antibody effectors) (FIGURE 1-2[20] and TABLE 1-2[19]). Some neural antibodies react with intracellular antigens and thus are nonpathogenic (with cytotoxic T cells as effectors), and others target cell surface antigens, such as receptors and channels, and have pathogenic effects.

Pathogenic mechanisms of neural IgG antibodies implicated include antigenic internalization (modulation), direct molecule inhibition without internalization, complement activation, disruption of protein-to-protein interactions, and antibody-dependent cellular cytotoxicity. Cell surface–reactive IgG binds to extracellular epitopes of ionotropic and metabotropic receptors, water channels, and neural adhesion proteins, the effects of which have been recapitulated in live neuronal and astrocytic cultures in vitro. For example, antibodies targeting α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, γ-aminobutyric acid $(GABA)_A$ receptor, and NMDA receptor, lead to neuronal dysfunction through IgG-mediated receptor cross-linking and internalization (modulation), which results in reduced cell-surface receptor density. However, $GABA_B$ receptor antibodies impair receptor function directly without causing receptor internalization. The disruption of protein-to-protein interactions by antibodies, and thus interference with the protein target's function, is likely the major mechanism of action in diseases that are primarily mediated by IgG4 antibodies, such as LGI1's protein-to-protein interaction with its receptor ADAM metallopeptidase domain 22. Antibody-dependent cell-mediated cytotoxicity and complement cascade activation have also been implicated in AQP4 immunity.[21] Animal models of the passive transfer of synaptic antibodies delivered directly to the central nervous system (CNS) compartment (in NMDA receptor encephalitis) or the periphery (CASPR2 encephalitis) have reproduced clinical and histopathologic findings of these diseases.

In recent years, postinfectious autoimmune encephalitides have been recognized, mainly after HSV-1 encephalitis.[22] It is hypothesized that local release of antigens on neuronal death leads to immune system activation and antigen-specific autoimmunity, rather than molecular mimicry. This phenomenon has also been reproduced in an animal model.[16] Other factors regulating CNS autoimmunity include interindividual differences in immune surveillance and activation at the blood-brain barrier (such as antigen-presenting cell activation of CNS-resident T cells and the extent of ingress of lymphocytes across the blood-brain barrier, blood-CSF barrier, and glia limitans) and the ability of autoantigen-specific B cells to bypass self-tolerance checkpoints in the bone marrow and periphery.[12]

CLINICAL PRESENTATIONS

Autoimmune neurologic disorders are almost always subacute in onset (over days to weeks, with significant impairment by 6 to 12 weeks) and rapidly progressive. Sometimes the symptoms can fluctuate initially, and there may even be temporary partial remissions. In this article, the authors review the core characteristics of autoimmune neurologic disorder phenotypes (TABLE 1-3); a

KEY POINTS

- Risk factors that should be considered when evaluating autoimmune neurologic disorders include cancer history, smoking history, other autoimmune disease history, and immune checkpoint inhibitor use for cancer.
- Some neural antibodies react with intracellular antigens and thus are nonpathogenic (with cytotoxic T cells as effectors), and others target cell surface antigens, such as receptors and channels, and have direct pathogenic effects.
- Pathogenic mechanisms of neural IgG antibodies include antigenic internalization (modulation), direct molecule inhibition without internalization, complement activation, disruption of protein-to-protein interactions, and antibody-dependent cellular cytotoxicity.

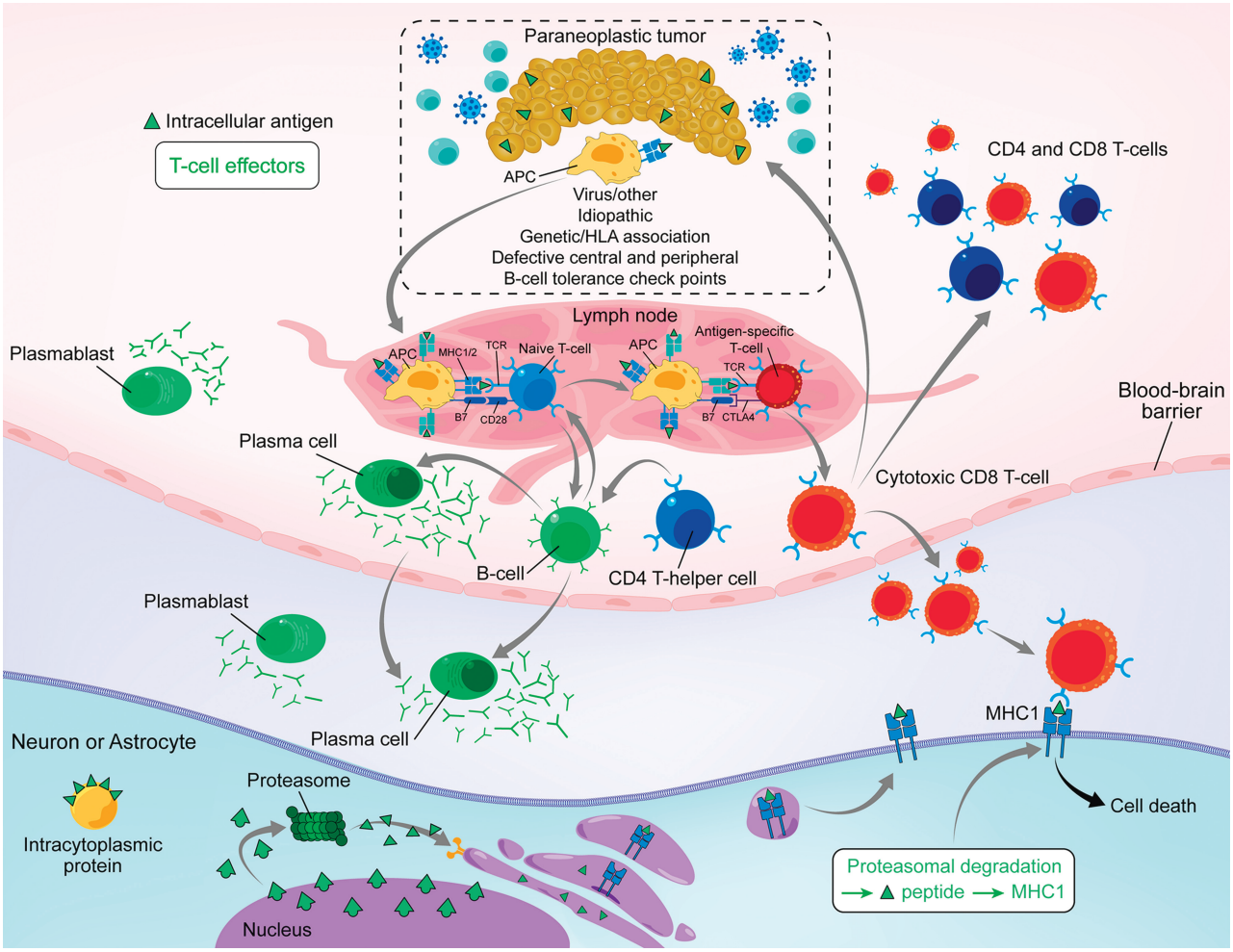

FIGURE 1-1
Immunopathogenic mechanisms of paraneoplastic and nonparaneoplastic (idiopathic) neural antibodies that target intracellular neural antigens (nuclear or cytoplasmic). In paraneoplastic autoimmunity, tumor-targeted immune responses are initiated by onconeural proteins expressed in the cytoplasm, nucleus, or nucleolus (*green triangle*) of certain tumors. These antigens are also expressed in neural cells and thus are coincidental targets. Dendritic antigen-presenting cells (APCs) capture, process, and present these cancer-derived neoantigens on major histocompatibility complex (MHC) molecules to naive T cells in the lymph nodes (*blue cells*). Recognition of intracellular neuronal antigens (*green triangle*) activates $CD8^+$ cytotoxic T cells (*red cells*). Intracellular antigens (*green triangles*) are not accessible to immune attack in situ, but peptides derived from intracellular proteins are displayed on upregulated MHC class I molecules in a proinflammatory cytokine milieu after proteasomal degradation and are then accessible to peptide-specific cytotoxic T cells (*red cells*). These cytotoxic $CD8^+$ T cells can cross the blood-brain barrier and cause direct cytotoxicity and irreversible neural cell death. Antibodies (*green Ys*) targeting nuclear or cytoplasmic antigens (produced by plasma cells and plasmablasts [*green cells*]) are detected in both serum and CSF but are not pathogenic. These antibodies are serum markers of this T-cell effector–mediated injury. In clinical practice, these antibodies serve as diagnostic markers of a T cell–predominant effector process (TABLE 1-1). Some examples of therapeutic strategies aimed at reducing disease-driving autoreactive cytotoxic T cells that are used include tumor removal and alkylating and other bone marrow–suppressant agents (eg, cyclophosphamide, mycophenolate mofetil, tacrolimus, cyclosporin). Future considerations include anti-CD52 monoclonal antibodies (eg, alemtuzumab), chimeric antigen receptor T-cell therapy targeting T-cell receptors (TCRs) on $CD8^+$ T cells, tolerization strategies, and α4-integrin monoclonal antibodies (eg, natalizumab).
CTLA4 = cytotoxic T-lymphocyte associated protein 4; HLA = human leukocyte antigen.

Neural Antibodies Against Intracellular Targets as Biomarkers for Central Nervous System Autoimmunity[ab]

TABLE 1-1

Antibody target	Median onset age	Male-to-female ratio	Clinical presentation	Tumor, antibody, and gene associations	Response to immunotherapy and cancer treatment and clinical outcome
ANNA-1 (Hu)	Mid 60s	1:1	Multifocal: sensory neuronopathy, limbic encephalitis, cerebellar ataxia, seizures, progressive encephalomyelitis (PEM), opsoclonus myoclonus, myelopathy, dysautonomia, gastrointestinal dysmotility (with or without pseudoobstruction)	80%: small cell lung cancer (SCLC), thymoma, neuroblastoma; amphiphysin, MAP1B, SOX1, ZIC4, DACH1 commonly coexist	50% of patients improve or stabilize with immunotherapy and cancer therapy
CRMP-5 (CV2)	Mid 60s	1:1.5	Multifocal: neuropathy, limbic encephalitis, cerebellar ataxia, PEM, optic neuritis and retinitis, chorea, myelopathy with or without tractopathy	80%: SCLC, thymoma; ANNA-1, amphiphysin, MAP1B, SOX1, ZIC4, DACH1 commonly coexist	50% of patients improve or stabilize with immunotherapy and cancer therapy; median survival is 10-20 months for SCLC, depending on tumor type
Amphiphysin	Mid 60s	1:1.5	Multifocal: PEM, limbic encephalitis, cerebellar ataxia, myelopathy, neuropathy, stiff person spectrum	80%: SCLC, breast cancer; CRMP-5, ANNA-1, VGCC commonly coexist	Some patients respond to immunotherapy, cancer therapy, or both; disease course is usually severe, and 40% of patients use a wheelchair after 6 months.
ANNA-2	65 years	1:3	Brainstem encephalitis, cerebellar ataxia, opsoclonus myoclonus syndrome, myelopathy, neuropathy, jaw dystonia, jaw spasm, and laryngospasm	80%: lung cancer, breast cancer; ANNA-1 commonly coexists	Median modified Rankin Scale (mRS) score at 1 year is 4 (patient unable to walk unassisted)
ANNA-3 (DACH1)	64 years	1:1.8	Multifocal: neuropathy, encephalopathy, cerebellar ataxia, myelopathy, dysautonomia	90%: neuroendocrine cancer, including SCLC; NIF, CRMP-5, ANNA-1, SOX1, MAP1B commonly coexist	75% of patients improve with immunotherapy, cancer therapy, or both
PCA-1 (Yo)	60s	1:20	Progressive cerebellar degeneration	90%: breast, ovarian, and müllerian cancer in females; gastrointestinal adenocarcinoma in males	Poor prognosis: most patients use a wheelchair within 3 months; median survival of 100 months for patients with breast cancer and 22 months for those with gynecologic cancer

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Antibody target	Median onset age	Male-to-female ratio	Clinical presentation	Tumor, antibody, and gene associations	Response to immunotherapy and cancer treatment and clinical outcome
PCA-2 (MAP1B)	Mid 60s	1:1	Neuropathy, cerebellar degeneration, limbic or brainstem encephalitis, ataxia, seizures, sleep disorders	80%: SCLC; CRMP-5, ANNA-1, DACH1 commonly coexist	54% of patients improve with immunotherapy; 70% reported some benefit after cancer therapy; median survival was 54 months
SOX1 (AGNA)	Variable age (mid 60s)	2.3:1	Lambert-Eaton myasthenic syndrome (LEMS), cerebellar ataxia, limbic encephalitis, neuropathy	90%: SCLC (especially highly associated with SCLC with LEMS); CRMP-5, ANNA-1, amphiphysin, DACH1, VGCC commonly coexist	For patients with SOX1 with LEMS: 60% have a partial remission only with immunotherapy; median survival is 15 months
ZIC4	Late 60s	9:1 (when isolated)	Progressive cerebellar degeneration mostly, multifocal disease (PEM), sensory neuronopathy	90%: SCLC (rarely ovarian and hematologic cancer); CRMP-5, ANNA-1, and P/Q-type VGCC (with LEMS) commonly coexist	Similar to ANNA-1 and CRMP-5
Ma1/Ma2 (Ta)	Ma1 and Ma2: 60s Ma2 only: late 30s	Ma1 and Ma2: 1:1.5 Ma2 only: 2.3:1	Ma1 and Ma2: progressive cerebellar degeneration, limbic encephalitis, brainstem or cerebellar encephalitis Ma2 only: limbic, diencephalic, and brainstem encephalitis, eye movement abnormalities, sleep disorders (excessive daytime sleepiness, narcolepsy, and cataplexy)	80%: Ma1 and Ma2: SCLC, gastrointestinal and breast cancer, lymphoma, testicular cancer 90% Ma2 only: germ cell tumors (seminoma, may be mediastinal metastasis)	Only 50% of patients improve or stabilize with immunotherapy and cancer therapy Mortality is high
KLHL11	Mid 40s	99:1	Rhombencephalitis (brainstem and cerebellar), hearing loss and tinnitus	80%: germ cell tumors (seminoma); LUZP4 *HLA-DQB1*02:01* and *HLA-DRB1*03:01* coexist	Poor prognosis: 25% of patients improve with immunotherapy and cancer therapy; 25% mortality at 1 year

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Antibody target	Median onset age	Male-to-female ratio	Clinical presentation	Tumor, antibody, and gene associations	Response to immunotherapy and cancer treatment and clinical outcome
LUZP4	Mid 40s	9:1	Rhombencephalitis (brainstem and cerebellar), limbic encephalitis, seizures, motor neuronopathy, and polyradiculopathy	85%: germ cell tumors (seminoma, commonly extratesticular), teratoma 100% if regressed testicular tumors are included; KLHL11, Ma2 coexist	75% of patients either stabilized or had improvement with immunotherapy + cancer therapy; 30% of patients used a wheelchair at last follow-up
PDE10A	70s	1.3:1	Movement disorder (including chorea), encephalopathy	85%: lung, renal, pancreatic cancer	Rare, high mortality
GFAP	50s	1:1	Encephalitis, meningoencephalitis, myelitis, optic disc edema; distinctive imaging pattern of cerebral radial perivascular enhancement	25%: teratoma, carcinoid, glioma, adenocarcinoma NMDA receptor, AQP4 coexist	80% of patients have good improvement with immunotherapy, median mRS score of 1.5 at 1 year 20-50% relapse
NIF	60s	3:2	Ataxia, encephalopathy, myeloneuropathy	For neurofilament light chain positivity: 88% have cancer (neuroendocrine carcinoma, small cell, Merkel cell hepatocellular)	77% of patients have immunotherapy response
GAD65	Mid 40s	1:3	Limbic encephalitis, stiff person syndrome, focal onset seizures, cerebellar ataxia, epilepsy, cognitive impairment, myelopathy, brainstem dysfunction	<10%: SCLC; neuroendocrine, thymic, and breast cancer; non-Hodgkin lymphoma; more likely in patients with limbic encephalitis $GABA_B$ receptor (with paraneoplastic neurologic syndrome) and $GABA_A$ receptor, glycine receptor (without cancer)	Sustained response to immunotherapy: 25% in epilepsy, 73% in stiff person spectrum disorders; complete immunotherapy response 1%; cerebellar ataxia and serum GAD65 antibody titre >500 nmol/L predict poor outcome

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Antibody target	Median onset age	Male-to-female ratio	Clinical presentation	Tumor, antibody, and gene associations	Response to immunotherapy and cancer treatment and clinical outcome
GRAF ARHGAP26	75 (with cancer), 36 (without cancer)	1:1	Limbic encephalitis; cognitive impairment specificity of antibody is unclear	40%: variable	Variable presentations and unclear outcome
ITPR1	Mid 60s	1:2.3	Cerebellar ataxia, peripheral neuropathy, encephalitis, and myelopathy specificity of antibody is unclear	35%: variable; breast, renal, and endometrial cancer	Variable presentations and unclear outcome
TRIM46 (little data on Trim9 and TRIM67)	Late 60s	1:2	Subacute cerebellar syndrome, encephalopathy, brainstem syndrome, limbic encephalitis, myelopathy, seizures	82%: varied, neuroendocrine lineage in half, SCLC most common	Poor immunotherapy response: most patients progress and die within 18 months of onset
AP3B2	40s	1:1.5	Subacute onset and rapidly progressive gait ataxia, myeloneuropathy, sensory peripheral neuropathy	No clear association	Poor immunotherapy response: immunotherapy may result in stabilization at best
Neurochondrin	Mid 40s	1:1.6	Cerebellar ataxia, brainstem disorder, myelopathy, small fiber neuropathy	<20%: no clear association	80% of patients use a wheelchair despite immunotherapy; cerebellar atrophy is progressive

AGNA = antiglial nuclear antibody; ANNA-1 = antineuronal nuclear antibody type 1; ANNA-2 = antineuronal nuclear antibody type 2; ANNA-3 = antineuronal nuclear antibody type 3; AP3B2 = adaptor-related protein complex 3, beta 2 subunit; AQP4 = aquaporin-4; CRMP-5 = collapsin response mediator protein 5; DACH1 = Dachshund family transcription factor 1; $GABA_A$ = γ-aminobutyric acid type A; $GABA_B$ = γ-aminobutyric acid type B; GAD65 = glutamic acid decarboxylase 65; GFAP = glial fibrillary acidic protein; GRAF ARHGAP26 = rho GTPase-activating protein 26; ITPR1 = inositol trisphosphate receptor type 1; KLHL11 = Kelch-like protein 11; LUZP4 = leucine zipper 4; MAP1B = microtubule-associated protein 1B; NIF = neuronal intermediate filament; NMDA = *N*-methyl-D-aspartate; PCA-1 = Purkinje cell cytoplasmic antibody type 1; PCA-2 = Purkinje cell cytoplasmic antibody type 2; PDE10A = phosphodiesterase 10A; SOX1 = SRY-box transcription factor 1; TRIM9 = tripartite motif containing protein 9; TRIM46 = tripartite motif containing protein 46; TRIM67 = tripartite motif containing protein 67; VGCC = voltage-gated calcium channel; ZIC4 = Zic family member 4.

[a] Data from Pittock SJ, et al, Autoimmune Neurology.[19]

[b] Testing is currently available on a service basis.

detailed review will follow in ensuing articles within this issue. The key feature of autoimmune neurologic disorders in the history is subacute onset with rapid progression.

Central Nervous System

Neurologic autoimmunity can affect various CNS levels, with presentations corresponding to the level or levels affected.

LIMBIC ENCEPHALITIS. Limbic encephalitis is characterized clinically by subacute onset and rapid progression of altered mental status, amnesia, seizures, and psychiatric symptoms. Bilateral mesial temporal T2 signal hyperintensities on MRI are typical (FIGURE 1-3A). The diagnosis is supported by elevated CSF white blood cell count and findings localizing to the temporal lobe on EEG (epileptic activity, slowing, or both).[1] A multitude of antibodies are associated with limbic encephalitis, which gives differentiation for the likelihood of a paraneoplastic cause, potential for treatment response, and prognosis. For example, ANNA-1 (anti-Hu) is typically associated with small cell lung cancer; responses to immunotherapy are often disappointing, and the overall prognosis is poor. In contrast, LGI1 antibody usually occurs in a nonparaneoplastic context; the responses to immunotherapy are brisk and meaningful and even have the potential to be curative. Although nonparaneoplastic, GAD65 antibody–associated limbic encephalitis responds poorly to immune therapies and tends to result in autoimmune epilepsy (chronic seizures).

AUTOIMMUNE SEIZURES. More limited forms of limbic encephalitis have been encountered, usually isolated seizures without cognitive impairment, accounting for one-third of all limbic autoimmune cases.[23] Patients typically have an absence of common risk factors for seizures, such as a history of head injury or family history of epilepsy, and are generally unresponsive to antiseizure medications. The pertinent antibodies are the same as for autoimmune encephalitis. Patients with LGI1 and CASPR2 antibodies have the best immunotherapy responses overall.

ENCEPHALITIS (EXTRALIMBIC). The term *extralimbic* is appropriate for clinical, radiologic, or EEG findings associated with neocortical temporal or extratemporal encephalitis localization, some of which are multifocal disorders. Extralimbic encephalitic disorders include autoimmune GFAP astrocytopathy, NMDA receptor encephalitis, $GABA_A$ receptor encephalitis, and dipeptidyl-peptidase–like protein 6 (DPPX) encephalitis.[24-27] Patients with autoimmune GFAP astrocytopathy present with either encephalitis, meningoencephalitis, or meningoencephalomyelitis. These patients experience one or more of the following: altered mood, psychosis, encephalopathy, blurred vision, headache, tremor, myelopathic findings, dysautonomia, and sometimes peripheral neuropathy. Paraclinical findings include an elevated CSF white blood cell count, diverse patterns of T2 signal abnormalities, and postgadolinium enhancement on brain MRI (characteristic linear enhancement running perpendicular to the corpus callosum, optimally appreciated on axial imaging) (FIGURE 1-3B). Approximately 25% of patients with autoimmune GFAP astrocytopathy have an accompanying neoplasm.

NMDA receptor encephalitis typically presents with a neuropsychiatric disorder (low mood, thought disorder, anxiety, mania) followed by a progressive course of encephalopathy, seizures, and dyskinesia that in severe cases evolves into autonomic instability and coma. Normal MRI of the brain and marked elevation of CSF white blood cell count (lymphocytic) are typical. Neoplasm (ovarian teratoma or testicular neoplasm) occurs in just under one-half of patients, with other cancer types found in patients older than 40 years.

KEY POINTS

- **The key feature of autoimmune neurologic disorders in the clinical history is subacute onset with rapid progression.**
- **Autoimmune encephalitis is typified by altered mental status, working memory difficulties, and often seizures. A forme fruste presenting with isolated seizures is relatively common.**
- **Common markers of limbic encephalitis include leucine-rich glioma inactivated protein 1 (LGI1), high-titer glutamic acid decarboxylase 65 (GAD65), and Hu antibodies. Common markers of nonlimbic encephalitic disorders include *N*-methyl-D-aspartate (NMDA) receptor and glial fibrillary acidic protein (GFAP) antibodies.**

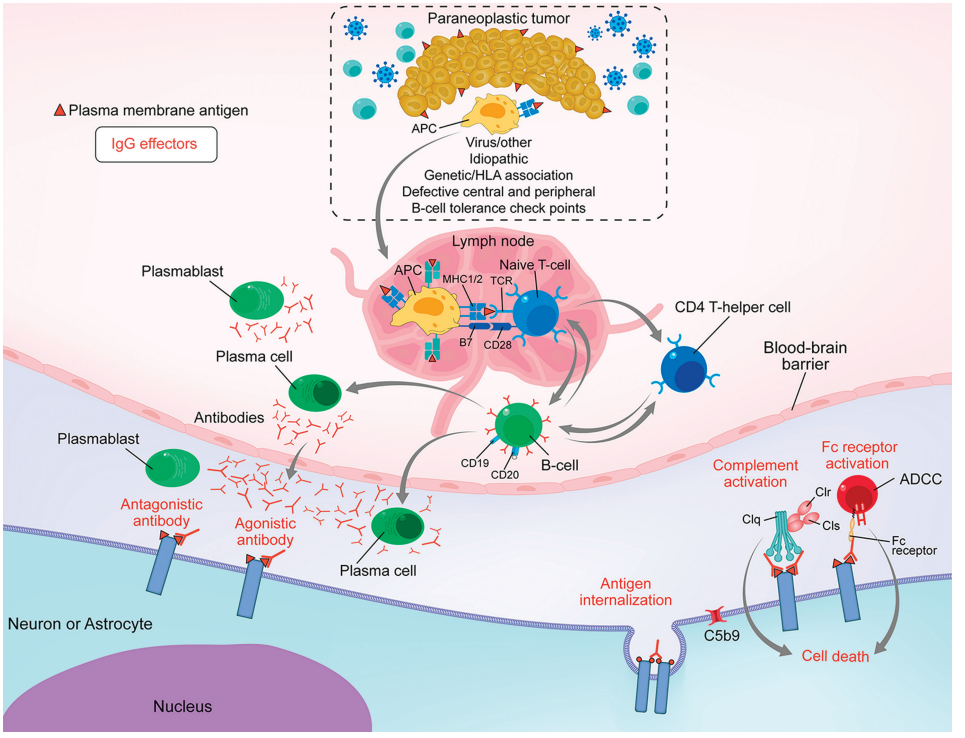

FIGURE 1-2

Immunopathogenic mechanisms of paraneoplastic and nonparaneoplastic (idiopathic) neural antibodies that target neural cell plasma membrane antigens. In paraneoplastic autoimmunity, tumor-targeted immune responses are initiated by onconeural proteins (*red triangle*) expressed in certain tumors. These antigens are also expressed on the cell surface of neural cells and are coincidental targets. The source of the antigen remains elusive in most cases. Plasma membrane antigens (*red triangle*) are presented by dendritic antigen-presenting cells (APCs) to naive T cells in the lymph nodes (*blue cells*). $CD4^+$ helper T cells then activate memory B cells and antibody-producing plasma cells or plasmablasts (*green cells*), driving antibody (*red Ys*) production and release. Antibodies (*red Ys*) targeting plasma membrane antigens (*red triangles*) are effectors of injury. These effector mechanisms include (1) receptor agonist or antagonist (competitive or allosteric antagonism) effects, (2) activation of the complement cascades resulting in complement-dependent cytotoxicity with the formation of a membrane attack complex to lyse the target cell (eg, aquaporin-4 [AQP4] IgG), (3) natural killer cells bind to the Fc domain of the target antigen with their FcγRIII receptors and induce antibody-dependent cellular cytotoxicity with the release of cytotoxic factors, (4) modulation of protein expression and function such as antigen-receptor crosslinking and internalization (antigenic modulation), thereby altering antigen density on the cell surface (eg, NMDA receptor antibodies disrupt NMDA receptor synaptic clusters and result in internalization and degradation), (5) protein-to-protein disruption (eg, leucine-rich glioma inactivated protein 1 [LGI1] antibodies disrupt the formation of a transsynaptic complex by inhibiting the interaction of LGI1 with ADAM metallopeptidase domain 23 [ADAM23] and ADAM metallopeptidase domain 22 [ADAM22]).

ADCC = antibody-dependent cellular cytotoxicity; HLA = human leukocyte antigen; MHC = major histocompatibility complex; TCR = T-cell receptor.

Data from Diamond B, et al, Nature Reviews Immunology.[20]

$GABA_A$ receptor encephalitis is typified by encephalopathy and prominent multifocal seizures accompanied by deep or subcortical white matter lesions (nonenhancing), often accompanied by thymoma. DPPX encephalitis is predominated by an encephalitic or encephalomyelitic phenotype. It is characterized by a triad of gastrointestinal disturbance (profuse diarrhea with early weight loss), symptoms of CNS hyperexcitability (muscle spasms and myoclonus), and encephalopathy. Head and spine MRI is typically normal.

ENCEPHALOMYELITIS. Patients with encephalomyelitis have symptoms localizing to both the cerebrum and spinal cord.[4] Some patients also have accompanying symptoms referable to dorsal root ganglia, nerve root, or peripheral nerve (encephalomyeloneuritis or encephalomyeloradiculitis). These multifocal disorders, exemplified by **CASE 1-1**, often have a paraneoplastic cause, most associated with small cell carcinoma in the setting of collapsin response mediator protein-5 (CRMP-5), ANNA-1, Purkinje cell cytoplasmic antibody type 2 (PCA-2) (also known as microtubule-associated protein 1B [MAP1B]), or amphiphysin antibodies. Other antibodies such as those targeting GFAP, MOG, and glycine receptors should also be included when considering the differential diagnosis for encephalomyelitis.

BRAINSTEM SYNDROMES. Brainstem encephalitis (rhombencephalitis) is a multimodal disorder that presents with one or more of the following: gait ataxia, postural instability, oscillopsia, vertigo, diplopia, dysarthria, dysphagia, cranial neuropathies, and sleep disorders, such as dream enactment, sleep apnea, and stridor. Some patients may also have higher cortical symptoms (seizures, encephalopathy). Progressive supranuclear palsy is often in the differential diagnosis, although the time course will generally be distinct (subacute for brainstem encephalitis, insidiously progressive for progressive supranuclear palsy), and typically there are nonprogressive supranuclear palsy–typical features with brainstem encephalitis, such as ptosis, atypical eye movement disorders, cranial neuropathies, jaw dystonia, and narcolepsy. Specific signs suggestive of certain brainstem encephalitides include jaw-clenching episodes with antineuronal nuclear antibody type 2 (ANNA-2 [also called anti-Ri antibody]) and deafness in men with KLHL11 autoimmunity (most of whom have seminoma). Brainstem T2 signal abnormalities may be observed in some patients (**FIGURE 1-3C**). Ataxic disorders may consist of pure cerebellar ataxias or may include a combination of ataxic and brainstem symptoms and signs (brainstem encephalitis).

RAPIDLY PROGRESSIVE CEREBELLAR ATAXIA. Patients with progressive cerebellar ataxia present with subacute onset and rapid progression of a pancerebellar disorder encompassing several of the following: oscillopsia (due to nystagmus), broad-based gait, ataxic dysarthria, and dysmetria. Multiple related antibodies have been characterized, with the most common being Purkinje cell cytoplasmic antibody type 1 (PCA-1) (anti-Yo), which is associated with breast and gynecologic adenocarcinoma, and GAD65 antibody (usually not associated with cancer) (**FIGURE 1-3D**). However, broad testing to cover the full range of antibodies should be considered (eg, Purkinje cell cytoplasmic antibody–Trotter/delta/notchlike epidermal growth factor-related receptor, metabotropic glutamate receptor 1 [MGLUR1], which are both associated with lymphoma,

KEY POINTS

- Autoimmune ataxic disorders may consist of pure cerebellar ataxias or may include a combination of ataxic and brainstem symptoms and signs (brainstem encephalitis).
- Rapid onset of several of the following signs and symptoms should prompt consideration of brainstem encephalitis: oscillopsia, speech and swallowing problems, postural instability, and craniocervical dystonia.
- Kelch-like protein 11 (KLHL11), Ma2, antineuronal nuclear antibody type 2 (ANNA-2 [anti-Ri]), Ig-like cell adhesion molecule 5 (IGLON5), GAD65, and myelin oligodendrocyte glycoprotein antibodies are common diagnostic biomarkers in patients with autoimmune brainstem encephalitis.

TABLE 1-2 **Neural Antibodies against Extracellular Targets as Biomarkers for Central Nervous System Autoimmunity[a,b]**

Antibody target and predominant pathogenic IgG class	Median onset age	Male-to-female	Clinical presentation	Oncologic and genetic associations	Response to immunotherapy and outcome
NMDA receptor, IgG1	20s	1:4	Limbic encephalitis, subacute neuropsychiatric disturbances (anxiety, psychosis), dyskinesias, catatonia, seizures (delta brush on EEG), central hypoventilation and autonomic instability, cognitive and memory deficits, movement disorders	Age and sex dependent, highest frequency of 50%; ovarian teratoma in young females aged 12-45 years, carcinomas in older adults; herpes simplex virus encephalitis may trigger	Majority of patients have a good outcome with early immunotherapy and early oophorectomy (in those with proven teratomas) Approximately 50% improve with first-line immunotherapy at 4 weeks Approximately 75% of nonresponders improve after second-line immunotherapy; at 2 years, 80% have modified Rankin Scale (mRS) score of 0-2, 15% relapse
LGI1, IgG4	Mid 60s	2:1	Limbic encephalitis, memory deficits, faciobrachial dystonic seizures, ictal piloerection, bradycardia, paroxysmal dizzy spells, sleep disturbances including insomnia and rapid eye movement sleep behavior, dysautonomia	<5% usually thymoma >90% with *HLA-DRB1*07:01*	>75% of patients have a good response to immunotherapy; at 2 years postdiagnosis and treatment, 33% of patients are fully recovered, 33% of patients are functionally independent but unable to work, 33% are disabled or dead, and 20% to 30% relapse
CASPR2, IgG4	Mid 60s	9:1	Morvan syndrome (peripheral nerve hyperexcitability, autonomic instability, encephalopathy), limbic encephalitis, Isaacs syndrome, neuromyotonia, seizures, painful peripheral neuropathy	10% thymoma, higher in patients with Morvan syndrome 90% with limbic encephalitis have *HLA-DRB1*11:01*	One-half of patients have a favorable or full response to immunotherapy; one-half of patients have partial or no response to immunotherapy; 1 in 10 patients die whereas 25% relapse

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Antibody target and predominant pathogenic IgG class	Median onset age	Male-to-female	Clinical presentation	Oncologic and genetic associations	Response to immunotherapy and outcome
$GABA_B$ receptor, IgG1	60s 40s	4:1 (mostly paraneoplastic) 1.5:1 (idiopathic)	Limbic encephalitis, status epilepticus, rapidly progressing dementia, ataxia, and opsoclonus-myoclonus syndrome	50% (rare in patients <50 years) Presence of coexisting KCTD16 antibodies increases the likelihood of an underlying cancer; small cell lung carcinoma, other neuroendocrine neoplasia	70% of patients have a favorable response to immunotherapy and cancer therapy; high rate (40%) of mortality usually related to cancer; 10% relapse
MOG, IgG1	20-30	1:1 (70% adult, 30% children)	MOG antibody–associated disease (MOGAD): optic neuritis, myelitis, brainstem syndromes, acute disseminated encephalomyelitis, cerebral cortical encephalitis, seizures, brainstem and cerebellar demyelinating attacks, progressive white matter damage (leukodystrophylike pattern)	<5%	20-50% of patients relapse; 70% of patients have a high likelihood of full recovery; 20% of patients have disability after first attack
AQP4, IgG1	40s	1:8	Neuromyelitis optica spectrum disorder: optic neuritis, myelitis, area postrema syndrome; less commonly: other brainstem syndromes, symptomatic narcolepsy, and acute diencephalic syndrome	<10%: Rare reports of thymoma and breast adenocarcinoma	Relapsing disease; in the context of older attack prevention therapies: at 5 years, 57% of patients are blind in 1 eye, 23% need a wheelchair, 9% mortality
AMPA receptor, IgG1	60s	1:2.3	Limbic encephalitis, seizures, acute confusion and memory deficits, behavioral changes	60%: thymic tumors, lung carcinoma, breast adenocarcinoma; presence of coexisting antibodies increases the likelihood of an underlying cancer	80% of patients have a favorable response to immunotherapy; 35% relapse; cancer-related mortality in 15%

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Antibody target and predominant pathogenic IgG class	Median onset age	Male-to-female	Clinical presentation	Oncologic and genetic associations	Response to immunotherapy and outcome
DPPX, IgG4	50s	2.3:1	Onset often with prominent diarrhea and weight loss, neuropsychiatric decline, central nervous system hyperexcitability, gastrointestinal symptoms due to autoimmune gastrointestinal dysmotility, progressive encephalomyelitis with rigidity and myoclonus (PERM), seizures, cognitive dysfunction, myoclonus, tremor sleep disturbance, spinal cord and cerebellar syndromes	<10%: hematologic malignancies	30% of patients show little or no improvement with immunotherapy; 10% mortality; 20% relapse
P/Q-type VGCC, IgG1	Bimodal age pattern	1:1	Lambert-Eaton myasthenic syndrome (LEMS), rapidly progressive cerebellar syndrome	50% (higher in patients with cerebellar dysfunction): small cell carcinoma, breast or gynecologic adenocarcinoma; with SOX1 antibody positivity, >90% small cell lung cancer (SCLC); association with HLA-DR3 and HLA-B7 in nontumor LEMS	Poor prognosis in patients with SCLC
PCA-Tr (DNER), IgG1	50s	4:1	Rapidly progressive cerebellar syndrome, limbic encephalitis	90%: Hodgkin lymphoma	Oncologic response is complete in 88% of patients; only 41% show significant neurologic improvement at the last follow-up after immunotherapy and cancer therapy

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Antibody target and predominant pathogenic IgG class	Median onset age	Male-to-female	Clinical presentation	Oncologic and genetic associations	Response to immunotherapy and outcome
MGLUR1, IgG1	Mid 50s	1.2:1	Rapidly progressive cerebellar syndrome, cognitive deficits, seizures, psychiatric symptoms, dysgeusia	<20%: hematologic malignancy	40% of patients have significant improvement with immunotherapy 37% have an mRS score >2 at last follow-up; relapse 20%, mostly after immunotherapy discontinuation
GlyR, IgG1	50s	1:1	PERM, stiff person spectrum disorders, status epilepticus	<15% (mostly thymoma, also lymphoma, including Hodgkin lymphoma, breast cancer, and melanoma)	Generally responsive to immunotherapy; 10% mortality; 15% relapse
$GABA_A$ receptor, IgG1	40s (also pediatric age group)	1:1	Encephalitis, generalized seizures, and status epilepticus, distinctive cortical-subcortical lesions on brain MRI, cognitive dysfunction, acute behavioral changes	25-30% (10% in children, 60-70% in adults); thymoma	Partial or complete recovery in 80% of patients with immunotherapy; mortality of 10% due to status epilepticus
MGLUR5, IgG1	30	1.5:1	Limbic encephalitis (Ophelia syndrome, encephalopathy, mood disturbances, seizures), sleep disorders, movement disorders	50%: Hodgkin lymphoma	Good response with near full recovery in one-half of patients after immunotherapy
IgLON5, IgG1 and IgG4	60s	1:2	Insidious: sleep disturbance, movement disorders, brainstem disorders, bulbar symptoms, ataxia, chorea, cranial neuropathies, hyperexcitability (myoclonus, cramps, fasciculations, startle), neuropsychiatric symptoms, dysautonomia	<10%	50-70% of patients have partial improvement with immunotherapy; median mRS score of 2.5 at 15 months; mortality approximately 30%
Neurexin-3α, IgG	Mid 40s	1:2	Encephalitis, confusion, seizures	None	Only partial response to immunotherapy

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Antibody target and predominant pathogenic IgG class	Median onset age	Male-to-female	Clinical presentation	Oncologic and genetic associations	Response to immunotherapy and outcome
Septin 5, IgG1	50s	3:1	Cerebellar ataxia, eye movement disorders	None	Only partial response to immunotherapy; most patients have residual disability
Septin 7, IgG1	70s	1:1	Encephalopathy, myelopathy, episodic ataxia, psychiatric symptoms (agitation, apathy, catatonia, disorganized thinking, and paranoia)	None	Some patients have good response to immunotherapy; many patients have residual disability

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AQP4 = aquaporin-4; CASPR2 = contactin-associated proteinlike 2; DNER = delta/notchlike epidermal growth factor-related; DPPX = dipeptidyl-peptidase–like protein 6; $GABA_A$ = γ-aminobutyric acid type A; $GABA_B$ = γ-aminobutyric acid type B; GlyR = glycine receptor; HLA = human leukocyte antigen; IgLON5 = Ig-like cell adhesion molecule 5; KCTD16 = potassium channel tetramerization domain containing 16; LGI1 = leucine-rich glioma inactivated protein 1; MGLUR1 = metabotropic glutamate receptor 1; MGLUR5 = metabotropic glutamate receptor 5; MOG = myelin oligodendrocyte glycoprotein; NMDA = *N*-methyl-D-aspartate; PCA-Tr = Purkinje cell cytoplasmic antibody Tr; SOX1 = SRY-box transcription factor 1; VGCC = voltage-gated calcium channel.

[a] Data from Pittock SJ, et al, Autoimmune Neurology.[19]

[b] Testing is currently available on a service basis.

septin 5 and inositol trisphosphate receptor-1). Certain accompanying clinical features may be clues to individual serologic diagnoses, such as ageusia in the setting of MGLUR1 ataxia, oscillopsia in patients with septin-5 antibody, and episodic symptoms or thymoma associated with CASPR2 autoimmunity. Rapid onset of several of the following signs should prompt consideration of brainstem encephalitis: oscillopsia, speech and swallowing problems, postural instability, and craniocervical dystonia. KLHL11, Ma2, ANNA-2 (anti-Ri), IgLON5, GAD65, and MOG antibodies are common diagnostic biomarkers.

OPSOCLONUS-MYOCLONUS SYNDROME AND OTHER HYPERKINETIC MOVEMENT DISORDERS. Opsoclonus-myoclonus syndrome is characterized symptomatically by whole-body tremulousness, unsteadiness, and oscillopsia, and, on examination, by multidirectional lightninglike eye movements (opsoclonus) and generalized polymyoclonus.[28] Ataxia, encephalopathy, and sleep disturbance may also occur. Opsoclonus and limb disorders, including orthostatic disorders, may also occur as isolated phenomena. In affected young children, underlying neuroblastoma may be found, sometimes with ANNA-1 (anti-Hu). Opsoclonus-myoclonus syndrome may have postinfectious or paraneoplastic causation. ANNA-2 with breast adenocarcinoma or small cell carcinoma are characteristic opsoclonus-myoclonus syndrome associations. Opsoclonus-myoclonus syndrome may also accompany encephalopathy, exemplified by some cases of NMDA receptor encephalitis. Autoimmune chorea or chorea-dystonia may arise subacutely as an isolated phenomenon across the age range.[29] Occasionally, patients have accompanying basal ganglial T2 signal abnormalities on MRI

(FIGURE 1-3E).[30] Paraneoplastic chorea usually occurs with small cell carcinoma and associated antibodies (eg, CRMP-5). Autoimmune chorea can also be associated with systemic lupus erythematosus (SLE) and antiphospholipid syndrome, and affected patients usually have good immunotherapy responses.

MYELOPATHY. Patients with paraneoplastic myelopathy present with a subacute or insidious onset of motor weakness, lower limb and truncal sensory symptoms, and bowel or bladder disturbance. MRI imaging may provide clues (tract-specific T2 signal change or postgadolinium enhancement) (FIGURE 1-3F) as may CSF (restricted-oligoclonal bands, although this may cause confusion with primary progressive multiple sclerosis). Associated antibody and cancer specificities include amphiphysin IgG, CRMP-5, and ANNA-1 in the setting of small cell carcinoma (or breast adenocarcinoma with amphiphysin IgG). Autoimmune myelitis associated with AQP4 or MOG antibodies presents subacutely and is usually accompanied by longitudinally extensive T2 signal abnormalities and gadolinium enhancement.[31] Occasionally, patients with AQP4 IgG–positive NMOSD may progress to neurologic nadir within hours, necessitating distinction from spinal cord stroke with the aid of MRI. Neoplastic accompaniments of paraneoplastic NMOSD, such as thymoma and breast and lung cancers, are reportedly associated with male sex and older onset age.

STIFF PERSON SYNDROME. Stiff person syndrome spectrum disorders usually occur as an idiopathic autoimmune disease (rather than paraneoplastic), presenting with symptoms and signs of CNS hyperexcitability, associated with antibodies reactive with GAD65 or alpha-1 subunits of glycine receptors.[32] Classic stiff person syndrome presents with lower truncal and bilateral lower extremity

Autoimmune Neurologic Phenotypes TABLE 1-3

Anatomy	Autoimmune phenotype
Retina	Paraneoplastic retinopathy
Optic nerve	Optic neuritis, chiasmitis
Cerebral cortex	Autoimmune encephalitis, limbic encephalitis, autoimmune seizures, meningoencephalitis, encephalomyelitis
Basal ganglia	Autoimmune chorea
Cerebellum	Autoimmune ataxia
Brainstem	Brainstem encephalitis (rhombencephalitis)
Spinal cord	Myelitis, transverse myelitis, paraneoplastic myelopathy, stiff person syndrome spectrum disorder
Autonomic nervous system	Autoimmune autonomic ganglionopathy, autoimmune autonomic neuropathy, autoimmune gastrointestinal dysmotility
Peripheral nerve	Radiculopathies, acute inflammatory demyelinating polyradiculoneuropathy, chronic inflammatory demyelinating polyradiculoneuropathy, sensory neuronopathy, peripheral neuropathy
Neuromuscular junction	Myasthenia gravis, Lambert-Eaton myasthenic syndrome
Muscle	Necrotizing myopathy, autoimmune myositis, rippling muscle disease

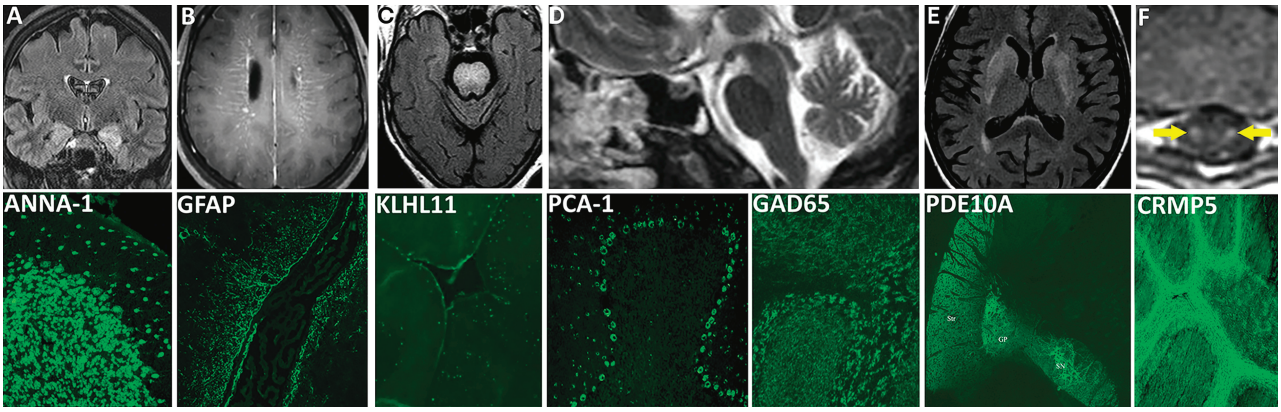

FIGURE 1-3
Examples of diverse neuroradiologic and antibody findings in autoimmune central nervous system diseases. Examples of diverse radiological findings (*top row*) encountered in autoimmune neurologic disease and examples of associated antibodies as recognized by indirect immunofluorescence assay (IFA) (*bottom row*). *A*, T2 coronal MRI demonstrates T2 hyperintensities in the mesial temporal lobes. Antineuronal nuclear antibody type 1 (ANNA-1 [anti-Hu]) was detected by IFA and confirmed by immunoblot; the patient had underlying small cell carcinoma in the setting of limbic encephalitis. *B*, Axial T1 postgadolinium MRI demonstrates linear radial perivascular enhancement in a patient with encephalitis. Glial fibrillary acidic protein (GFAP) IgG was detected by IFA and confirmed by GFAP-specific cell-based assay. *C*, A patient with brainstem encephalitis had T2 signal change in the pons on axial FLAIR MRI, and Kelch-like protein 11 (KLHL11) antibody was detected by IFA (cell-based assay confirmed). *D*, Sagittal T2 MRI demonstrates cerebellar atrophy, typical of autoimmune ataxia, and two of the many antibodies potentially detectable in this scenario (Purkinje cell cytoplasmic antibody type 1 [PCA-1] and glutamic acid decarboxylase 65 [GAD65]). PCA-1 is typically paraneoplastic and has a worse prognosis than GAD65. This illustrates that for any given neurologic phenotype, there are usually diverse antibody possibilities, necessitating a broad profile-based approach to testing. *E*, A patient with chorea-dystonia and renal cell carcinoma, after checkpoint inhibitor cancer therapy, had T2 hyperintensities in the basal ganglia on axial T2 fluid-attenuated inversion recovery (FLAIR) MRI, and phosphodiesterase 10A (PDE10A) antibody (basal ganglial-reactive) on IFA, cell-based assay confirmed. *F*, Axial T1 postgadolinium MRI of the spinal cord demonstrates gadolinium enhancement restricted to lateral tracts (*arrows*), typical of paraneoplastic myelopathy, which could be associated with diverse antibodies, exemplified by collapsin response mediator protein-5 [CRMP-5] IgG (confirmed by enzyme-linked immunosorbent assay [ELISA] or blot).

muscle rigidity and spasms, with spasms frequently accompanied by injurious falls. Startle responses are exaggerated and nonhabituating and can be the precipitant of whole-body spasms and falls. Partial stiff person syndrome phenotypes of one limb or hemi-body or isolated to the trunk also occur. In rare cases of stiff person syndrome, usually in elderly patients, GAD65 antibodies have a paraneoplastic association (lung or breast carcinomas or thymic tumors). Glycine receptor autoimmunity is comparatively rare and is associated with the progressive encephalomyelitis with rigidity and myoclonus phenotype and is less commonly associated with the stiff-limb or classic presentations. Approximately 10% of patients with stiff person syndrome are seronegative.[33]

Peripheral Nervous System

Autoimmunity can affect various peripheral nervous system levels, and much like CNS autoimmunity the presentation is determined by the level or levels affected.

CASE 1-1

A 47-year-old woman with a 30-pack-year smoking history developed subacute vision loss in both of her eyes (black clouds, blurred vision). Ophthalmic evaluation revealed bilateral papillitis, with a cellular infiltrate in the anterior chamber. Histology from a vitreous biopsy disclosed an inflammatory infiltrate. A combination of oral and intraocular corticosteroids was followed by improvement in vision. She then developed radicular lower extremity pain and balance difficulties. Neurologic examination revealed allodynia over the right side of her trunk, areflexia, preserved sensation, and impaired gait. Her pain partially improved after corticosteroid treatment, but not her gait disorder. Given her smoking history and multifocal neurologic disorder, antibody testing was performed. Collapsin response mediator protein 5 (CRMP-5) IgG was detected in serum and CSF by tissue-based indirect immunofluorescence assay and confirmed by CRMP-5-specific Western blot. A fludeoxyglucose-avid 1 cm right lung nodule was detected on positron emission tomography (PET)-CT. Biopsy histology revealed small cell carcinoma, and she was treated with chemotherapy.

The patient remitted from her cancer and remained well, although with residual imbalance, for 2 years. At that time, she developed dysarthria, more weakness in her extremities, worsening imbalance, early satiety, postprandial vomiting, abdominal bloating, and constipation. Her examination revealed new cerebellar ataxia proximal limb weakness and areflexia. PET-CT revealed cancer recurrence. EMG revealed features of Lambert-Eaton myasthenic syndrome (LEMS). CRMP-5 IgG was again detected in serum and CSF, and P/Q-type voltage-gated calcium channel antibodies were also present in her serum. Neurologic improvement occurred upon treatment with a combination of symptom-directed therapies (ie, 3,4 diaminopyridine and pyridostigmine), corticosteroids, and intravenous immunoglobulin (IVIg) over 3 months; however, her cancer did not respond to treatment, and she died.

COMMENT

Autoimmune neurologic disorders, particularly those with paraneoplastic etiology, often present with a multifocal phenotype, or a multifocal phenotype evolves. Some presentations are antibody typical (eg, ophthalmitis with CRMP-5 IgG, LEMS with P/Q-type voltage-gated calcium channel antibodies), whereas others are more nonspecific but are typical of paraneoplastic disorders (eg, encephalomyeloneuropathy). In the absence of Class I evidence, physician-selected combinations of immunotherapy and symptom-directed therapies can bring about improvements in neurologic symptoms.

PERIPHERAL NEUROPATHIES. Length-dependent neuropathy or polyradiculoneuropathies may arise as autoimmune diseases in isolation or in the setting of an encephalomyeloneuropathic disorder. These are typically paraneoplastic in etiology.[34] CRMP-5 polyradiculoneuropathy presents as an asymmetric painful axonal neuropathy, whereas amphiphysin autoimmunity has a more symmetric phenotype. In contrast, MAP1B paraneoplastic neuropathy is usually a polyradiculoneuropathy, although it is generally painless. Oncologic associations are usually small cell carcinoma, except for amphiphysin IgG, which is typically associated with breast adenocarcinoma. Sensory ganglionopathy or neuronopathy is a high-risk paraneoplastic phenotype, mostly associated with anti-Hu (ANNA-1), but it is known to occur also with nonparaneoplastic Sjögren syndrome. These patients present with profound gait disturbance and sometimes writhing finger movements (pseudoathetosis) due to sensory ataxia. Demyelinating neuropathies are usually nonparaneoplastic and include disorders such as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and some closely related disorders with associated antibodies (neurofascin 155, contactin-associated proteinlike 1, or leucine-rich repeat LGI family member 4).[35-37]

AUTONOMIC NEUROPATHY. Features of autoimmune dysautonomia include light sensitivity (from mydriasis), orthostatic hypotension, heat intolerance due to anhidrosis, erectile dysfunction, urinary retention, and gastrointestinal dysmotility.[38] Gastrointestinal symptoms include abdominal distension, cramping, nausea, vomiting, constipation, and weight loss without mechanical obstruction. The classic autoimmune dysautonomia paraneoplastic association is with ANNA-1 (anti-Hu), and it usually occurs in the setting of small cell carcinoma or occasionally other cancer types, including thymoma.[39] Autoimmune autonomic ganglionopathy specifically refers to autoimmune dysautonomia that occurs with ganglionic nicotinic acetylcholine receptor antibody, which is usually not paraneoplastic, although diverse adenocarcinomas, small cell carcinoma, and thymoma are occasionally encountered. Autoimmune autonomic neuropathies can present with diverse manifestations (pandysautonomia) or limited disorders such as gastrointestinal dysmotility.

NEUROMUSCULAR JUNCTION DISORDERS. Autoimmune myasthenic syndromes present with muscle weakness, ranging from fatigable ptosis and diplopia in ocular myasthenia gravis to diffuse generalized myasthenic syndromes.[40] These are mostly acetylcholine receptor antibody associated, and a minority are muscle-specific tyrosine kinase (MuSK) antibody associated (usually with a bulbar phenotype). Thymoma or thymic carcinoma is encountered in 10% to 15% of patients who are acetylcholine receptor antibody positive. The presence of dysautonomia (dry mouth and erectile dysfunction in particular) and areflexia facilitated by exercise in patients with LEMS as opposed to normal-to-brisk reflexes in those with myasthenia gravis, may provide differentiating clinical clues. Small cell carcinoma is found in 50% of patients with LEMS and even more commonly among smokers older than 50 years with weight loss, bulbar involvement, and erectile dysfunction. P/Q-type voltage-gated calcium channel antibodies are the most sensitive

antibody biomarker for LEMS, and antiglial and antineuronal nuclear antibodies (antiglial nuclear antibody or SRY-box transcription factor 1 IgG) or ANNA-1 positivity have high positive predictive value for small cell carcinoma in patients with LEMS.[41]

NEUROMYOTONIA. Autoimmune peripheral nerve excitability, or neuromyotonia, presents with limb stiffness, muscle cramping, and muscle twitching (due to fasciculations or myokymia).[42] Autonomic dysfunction may coexist in patients who are positive for LGI1 or CASPR2 antibodies. Morvan syndrome is a multifocal disorder characterized by insomnia (termed *agrypnia excitata*), neuromyotonia, encephalopathy, and seizures. Patients with Morvan syndrome are usually CASPR2 antibody positive, and one-half of patients have thymoma.

MYOPATHY. Dermatomyositis is a form of immune-mediated myopathy with some malignancy risk (15% to 20%) from diverse cancer types. Affected patients develop both weakness affecting proximal limb muscles and cutaneous stigmata (periorbital heliotrope rash or purpuric papules of the dorsal fingers [*Gottron papules*]). Antibody biomarkers include nuclear matrix protein 2, transcription intermediary factor 1 gamma, and small ubiquitin-like modifier 1 activating enzyme subunit. These are detected more commonly among patients with disorders that have a paraneoplastic cause.[43] Necrotizing autoimmune myopathy is usually a severe myopathic disorder associated with signal recognition particle antibody (sometimes paraneoplastic, with gastrointestinal adenocarcinoma association) or 3-hydroxy-3-methylglutaryl coenzyme A HMG-CoA reductase antibody. Rippling muscle disease is a newly recognized autoimmune myopathy subtype associated with caveolae-associated protein 4 antibodies.[44]

DIAGNOSTIC CRITERIA

Criteria and guidelines to support diagnostic practice in autoimmune neurology have emerged in recent years. Some have utility for determining the level of certainty of various diagnoses such as NMOSD, MOG antibody–associated disease (MOGAD), autoimmune encephalitis, and autoimmune ataxia.[1,45-47] Others assist in predicting the likelihood of antibody positivity and treatment responses, whereas others assist in predicting the likelihood of a paraneoplastic cause.[4,48] There can be exceptions to these rules and gray areas are generally emphasized in possible criteria, and therefore diagnostic criteria are not a substitute for clinical judgement.

For example, guideline criteria for diagnosing autoimmune encephalitis were published in 2016.[1] These permit assessment of patients with subacute onset altered mental status, short-term memory loss, or psychiatric symptoms complemented by key examination findings, MRI, and CSF white cell count to reach at least a diagnosis of possible autoimmune encephalitis. In addition, CSF IgG index and oligoclonal bands, EEG, brain biopsy, and antibody test results can further refine diagnostic certainty to probable or definite autoimmune encephalitis. Specificity is assured by the exclusion of alternative diagnoses. However, these criteria do not capture all patients, such as patients presenting with seizures only, patients presenting with brainstem encephalitides, and patients with rare atypical seronegativity, in whom a diagnosis may be possible upon response to immunotherapy.[49]

KEY POINTS

- **Autoimmune autonomic neuropathies can present with diverse manifestations (pandysautonomia) or limited disorders such as gastrointestinal dysmotility.**
- **Diagnostic criteria for autoimmune encephalitis, paraneoplastic disorders, and autoimmune demyelinating diseases aid diagnostic assessment and clinical trial design.**

DIFFERENTIAL DIAGNOSIS

Neurologic autoimmunity needs to be considered as one of many potential causes of subacute-onset neurologic dysfunction. The list of disorders to be considered varies according to neurologic localization.[50] For instance, when considering possible infectious disease alternatives for limbic encephalitis, viral disorders such as HSV-1 and human herpesvirus 6 feature prominently, whereas for brainstem encephalitis both listeria monocytogenes and various herpes viruses are considered. Broad categories of subacute onset neurologic disorders include infection, primary and secondary neoplasia, endocrinopathies (eg, Addison disease), demyelinating disease (eg, multiple sclerosis), infiltrative inflammatory diseases (eg, neurosarcoidosis, IgG4 disease, histiocytosis), connective tissue disease (eg, SLE), celiac disease, other systemic immune-mediated disorders (eg, autoinflammatory syndromes), vasculitis, other vasculopathies (eg, dural arteriovenous fistulae), nutritional deficiency states (eg, deficiency of vitamin B_{12}), and some degenerative disorders (eg, rapidly progressive dementias, such as Creutzfeldt-Jakob disease, or occasionally dementia with Lewy bodies or Alzheimer disease).

ASSESSMENT

In patients with suspected autoimmune neurologic disease, there are two components to the assessment: (1) defining the neurologic phenotype and (2) defining the immunologic profile. Once the comprehensive history and examination are recorded, adjunctive paraclinical neurologic tests may be undertaken to fully define the phenotype or to confirm the autoimmune diagnosis.

Defining the Neurologic Phenotype

Radiographic and neurophysiologic tests assist in defining the phenotype and provide a baseline for future comparison, particularly postimmunotherapy.

MAGNETIC RESONANCE IMAGING. MRI imaging is widely used to evaluate brain and spinal cord disorders, principally relying on T2-weighted, fluid-attenuated inversion recovery (FLAIR), and T1 postgadolinium images.[51] Information derived from imaging needs to be integrated with clinical, EEG, and CSF data.[52] For example, in limbic encephalitis, which has a subacute onset, bilateral T2 hyperintensity of the mesial temporal lobes is typical, occasionally accompanied by contrast enhancement (FIGURE 1-3). Unilateral mesial temporal abnormalities, accompanying a more insidious course of memory loss, should raise concern for CNS tumors. Also, normal imaging does not rule out an autoimmune diagnosis. For example, in patients with NMDA receptor encephalitis, normal brain imaging is the most common finding, whereas a periventricular radial pattern of enhancement is found in patients with autoimmune GFAP astrocytopathy (FIGURE 1-3B), and multifocal deep white matter and juxtacortical and cortical lesions on FLAIR are typical of $GABA_A$ receptor encephalitis.[53,54] The characteristic radiologic feature of paraneoplastic myelitis is longitudinally extensive, tract-specific T2 signal change of dorsal or lateral columns, sometimes accompanied by enhancement postgadolinium (FIGURE 1-3F).[55] Nerve root enhancement may occur in paraneoplastic myeloneuropathy.[56] For suspected immune-mediated myopathies, MRI can aid in the localization of an affected muscle for biopsy and may aid in the distinction of different myopathy subtypes.

NEUROPHYSIOLOGY. EEG can show generalized slowing typical of encephalopathy and focal or multifocal seizures in patients with encephalitis or autoimmune seizures. The EEG finding known as extreme delta brush pattern has been reported in NMDA receptor encephalitis, generally among patients in an ICU with coma.[57] Nerve conduction studies and EMG aid in the classification of neuropathy (axonal versus demyelinating). Needle EMG can identify myopathic features, including fibrillation potentials indicative of muscle fiber necrosis.[58] Compound muscle action potential (CMAP) amplitude increment following exercise may be observed in patients with LEMS, and CMAP decrement with slow repetitive stimulation may be found in patients with LEMS or myasthenia gravis. Continuous motor-unit activity in lumbar paraspinal muscles on EMG, agonist-antagonist cocontraction, and increased exteroceptive and acoustic startle responses are encountered in patients with stiff-person syndrome. Stimulus-induced after discharges (on nerve conduction studies) and spontaneous firing of doublet or multiplet motor unit discharges (on EMG) are encountered in autoimmune peripheral nerve hyperexcitability.

Defining the Immunologic Profile

Routine CSF parameters and esoteric antibody tests assist in determining the presence of an autoimmune diagnosis.

CEREBROSPINAL FLUID. Routine findings on CSF supportive of an autoimmune neurologic disorder include elevated white cell count, the presence of CSF-exclusive oligoclonal bands (or kappa free light chains), or elevated CSF IgG index or synthesis rate.[59] In some patients, particularly those with known cancer or clinical or radiologic evidence of meningeal disease, cytology can help exclude carcinomatosis or lymphomatosis as alternative causes of neurologic dysfunction. There are no specific CSF glucose findings among patients with autoimmune disorders, but CSF glucose may be low in the setting of alternative diagnoses (infection, neurosarcoidosis, or cancer). Normal CSF findings do not exclude neurologic autoimmunity.[60] Cytokine-chemokine CSF profiles are now available and appear to be mechanistically informative within groups of patients with certain disease states as compared with others (eg, LGI1 encephalitis versus CASPR2 encephalitis).[61] In the future, these profiles may be clinically informative for individualized molecule-directed monoclonal antibody therapeutic approaches (eg, IL-6-receptor antagonist).

ANTIBODY TESTS. Neural IgG antibodies are increasingly important in the diagnosis of autoimmune neurologic diseases (TABLE 1-1, TABLE 1-2, and FIGURE 1-4).[62] The number of analytes has grown significantly over time and is ever-changing.[63] Therefore, it is challenging for individual clinicians to accurately select the appropriate antibodies to order in many cases. Therefore, the authors advocate for a neurologic phenotype-based profile approach to testing patients (FIGURE 1-4). This phenotype-based approach means there is variation in terms of specimens recommended for testing and the number of pertinent antibodies. For example, for a patient with optic neuritis, just 2 antibodies (AQP4 and MOG antibody) tested in serum suffices to be comprehensive. In contrast, for patients with autoimmune encephalitis, testing of serum and CSF for 15 or more antibodies is needed to be comprehensive. Depending on the assay used, some of those antibodies are more sensitively

KEY POINTS

- Before establishing the diagnosis of autoimmune neurologic disorders, it is critically important to consider and exclude alternative causes of subacute onset neurologic disorders, such as tumors, metabolic disorders, endocrinopathies, vitamin deficiency states, other inflammatory diseases, and some rapidly progressive degenerative disorders.
- In patients with autoimmune neurologic disease, the first component of the assessment is further defining the phenotype using neuroimaging, neurophysiology, and neuropsychometric testing where appropriate. The second component is defining the immune profile using antibody testing in serum and CSF as well as inflammatory markers in CSF such as white cell count and oligoclonal bands.

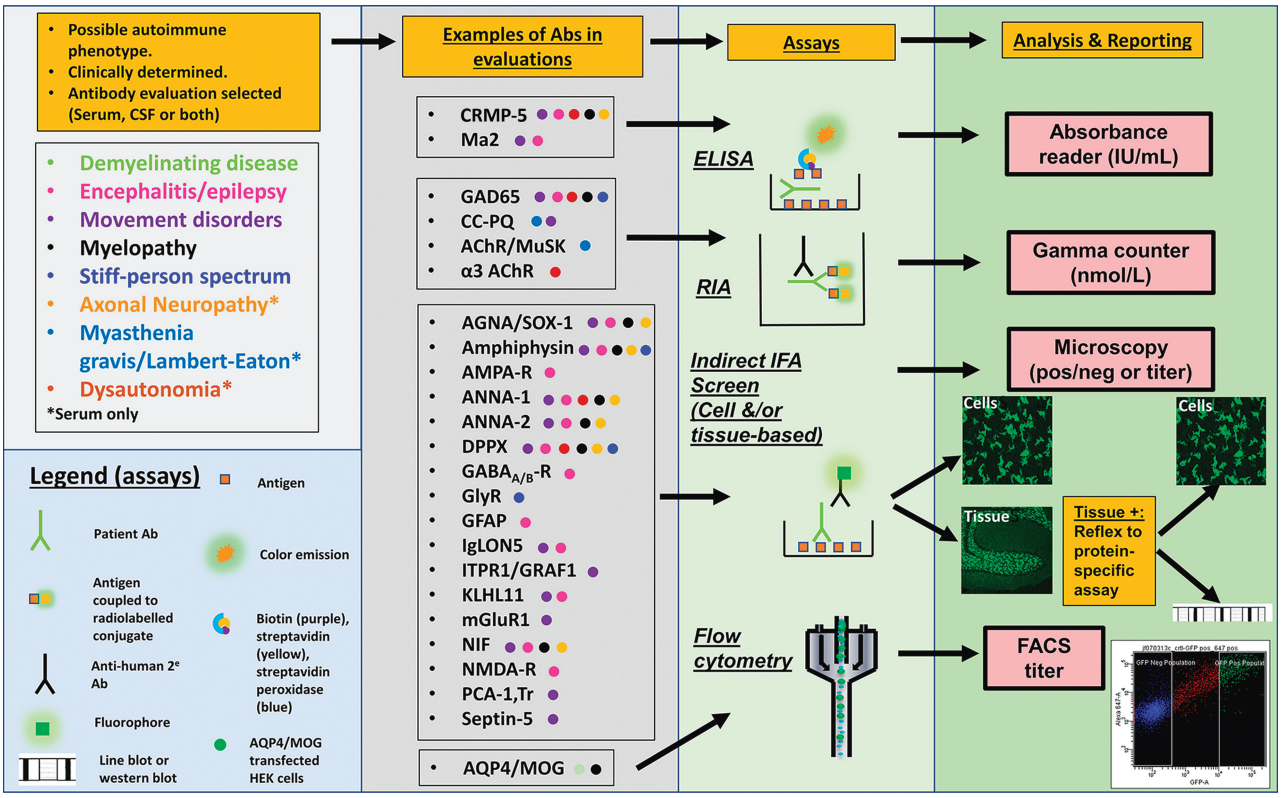

FIGURE 1-4

Neuroimmunology laboratory workflow. The first column shows evaluations. Based on phenotype, one serum and one CSF evaluation should be selected. The second column shows examples of antibodies (TABLE 1-1 and TABLE 1-2) and associated evaluations. The third column shows assays used for antibody detection, and the fourth column shows reported antibody values. For immunofluorescence assay (IFA), some analytes (eg, leucine-rich glioma inactivated protein 1 [LGI1]) are best detected by cells, whereas others can be detected by tissue-based assay and then confirmed by cell-based assay (eg, glial fibrillary acidic protein [GFAP] IgG) or blot (eg, antineuronal nuclear antibody type 1 [ANNA-1 (anti-Hu)]). Cells are cell-line transfected with the antigen of interest, and the tissue is rodent-brain based.

Ab = antibody; AChR = acetylcholine receptor; AGNA = antiglial nuclear antibody; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ANNA-2 = antineuronal nuclear antibody type 2; AQP4 = aquaporin-4; CC-PQ = P/Q-type voltage-gated calcium channel; CRMP-5 = collapsin response mediator protein-5; DPPX = dipeptidyl-peptidase-like protein 6; ELISA = enzyme-linked immune sorbent assay; FACS = fluorescence-activated cell sorting assay; GABA = γ-aminobutyric acid; GAD65 = glutamic acid decarboxylase 65; GlyR = glycine receptor; GRAF1 = GTPase regulator associated with focal adhesion kinase-1; HEK = human embryonic kidney; IgLON5 = Ig-like cell adhesion molecule 5; ITPR1 = inositol 1,4,5-trisphosphate receptor type 1; KLHL11 = Kelch-like protein 11; mGluR1 = metabotropic glutamate receptor 1; MOG = myelin oligodendrocyte glycoprotein; MuSK = muscle-specific tyrosine kinase; NIF = neuronal intermediate filament; NMDA-R = *N*-methyl-D-aspartate receptor; PCA-1,Tr = Purkinje cell cytoplasmic antibody Tr; RIA = radioimmunoprecipitation assay.

detected in serum than CSF (eg, LGI1 antibody, with retained specificity, exemplified by CASE 1-2), and with others sensitivity and specificity are both optimal in CSF (eg, GFAP and NMDA receptor antibodies).[14,64] For NMOSD, the sensitivity of testing for AQP4 IgG is high (greater than 80%), but for all other phenotypes (eg, encephalitis) the sensitivity for individual antibodies is low. Hence, profile-based testing is recommended, rather than testing for individual antibodies. Even in a tertiary referral center with its own specialized clinic and

diagnostic laboratory, seronegative cases among those meeting definite or at least possible autoimmune encephalitis criteria were 13% and 41%, respectively.[49]

Tissue-based indirect immunofluorescence or immunohistochemistry, cell-based assays, enzyme-linked immunosorbent assay (ELISA), and radioimmunoprecipitation assays serve as screening tools for neural antibodies (FIGURE 1-4). For antibodies meeting criteria by tissue-based assays, specificities need to be confirmed by antigen-specific methods, such as blots (line blots or

CASE 1-2

A previously well 67-year-old man repeatedly dropped items from his right hand. He noted that the items seemed forced from his hand. His spouse noted an ipsilateral facial twitch synchronous with him dropping items. His primary care provider observed an episode during which his right arm appeared to jerk and referred him to a neurologist. The attacks increased in frequency to 20 times per day. Some were preceded by the sensation of a warm feeling rushing upwards through his body. About 1 month into his illness, he began to develop some symptoms of episodic right-sided piloerection. He had neither cognitive nor psychiatric symptoms, nor did he have personality change. His neurologist observed these events to be faciobrachial dystonic seizures. Routine EEG and brain MRI were normal. CSF revealed normal white blood cell count and mildly elevated protein of 50 mg/dL (normal is less than 35 mg/dL). Trials of levetiracetam and lacosamide did not reduce seizure frequency. Leucine-rich glioma inactivated 1 (LGI1) IgG antibody was detected in serum by fixed cell–based assay. CSF antibody testing was negative. He was diagnosed with autoimmune seizures (faciobrachial dystonic seizures) due to LGI1 antibodies. He started IV methylprednisolone (1000 mg per day for 5 days). After day 3, the attacks ceased, but 1 week after completing corticosteroids the faciobrachial dystonic seizures resumed. The patient received further methylprednisolone infusions for 5 days, followed by weekly infusions, and then he was slowly tapered to zero over 9 months.

COMMENT

Faciobrachial dystonic seizures are a distinct phenotype practically pathognomonic for LGI1 encephalitis. Of patients with this condition, 80% have seizures at presentation, often as an isolated presentation, without CSF or radiologic clues to autoimmunity. The subacute onset and rapid progression in the absence of traditional risk factors for epilepsy prompted testing for neural antibodies. Depending on the assay used, some neural antibodies are more readily detected in serum (eg, LGI1), whereas others are more sensitively and specifically detected in CSF (eg, NMDA receptor). Autoimmune seizures usually do not respond to antiseizure medications, but some are immunotherapy-responsive. LGI1 encephalitis is seemingly the most reliably steroid responsive, although short courses of treatment do not suffice. Clinical trials are underway to evaluate satralizumab (interleukin 6 [IL-6] receptor antagnoist) as a treatment.

CASE 1-3

A 75-year-old woman with a history of autoimmune thyroid disease, for which she has been treated with levothyroxine therapy and stable for 10 years, was brought to the emergency department by her daughter with reports of sudden cognitive change. Her daughter had previously noted some mild memory decline in her mother but noted a major change in the 9 months since she had last visited her family. On examination, the patient was disoriented to time and place, her digit span was 5 out of 7, and she registered four words easily. After 5 minutes, she recalled zero out of four words initially registered. Her routine laboratory work including complete blood cell count with differential, C-reactive protein, complete metabolic panel, vitamin B_{12}, folate, and thyroid function tests were within normal limits. Thyroid peroxidase antibodies returned positive at 400 IU/mL (normal is less than 5 IU/mL). The patient was admitted to the hospital for further evaluation.

The following day, a brain MRI was performed and revealed generalized atrophy, most prominently in the hippocampi bilaterally, 40% of predicted volume for age, without T2 signal change or enhancement. CSF revealed a white cell count of 1/μL (normal is 5/μL or lower), protein of 50 mg/dL (normal is 35 mg/dL or lower), and negative oligoclonal band testing. Interictal EEG recording demonstrated normal alpha rhythm without slowing or epileptiform discharges. The patient received 1 g of IV methylprednisolone daily for 5 days. Almost immediately her attention, mood, and walking speed (although not her memory) seemed to improve, but this response waned by day 6 of hospitalization. On further questioning of the patient's husband, she had a steady decline in cognitive function over several years, and this had progressed to a loss of function in activities of daily living (eg, forgetting to turn the stove off, forgetting peoples' names, getting lost while driving) within the past 6 months. One week into her hospitalization, CSF antibody test results returned negative, but amyloid-β (1-42) was low, and both total tau and phosphorylated tau were elevated. A diagnosis of probable Alzheimer disease was made.

COMMENT

Obtaining an accurate history at onset is critical to determining the likelihood of an autoimmune cause of cognitive dysfunction. As in the scenario described, this may be challenging with disparate accounts of symptoms from various family members. The absence of a subacute onset and lack of supportive findings on MRI, CSF, and EEG determines that the patient did not fulfill the criteria for possible autoimmune encephalitis. MRI findings and the CSF amyloid-β and tau findings were supportive of a neurodegenerative diagnosis (Alzheimer disease). Thyroid antibodies are common in the general population, particularly in patients with a history of autoimmune thyroid disease, and their presence is a frequent contributor to autoimmune encephalitis misdiagnosis. Clinical responses to corticosteroid treatment can be difficult to interpret in some patients, owing to short-lived subjective improvements in mood and alertness attributable to hypercortisolemia.

Western blots), radioimmunoprecipitation assays, or ELISA usually for intracellular antigens and transfected cell-based assays (indirect immunofluorescence microscopy or flow cytometry) for plasma membrane antigen–directed antibodies. Reliance on commercial line blots alone is not recommended because of the propensity for false-positive results, and correlation with tissue-based testing is advised.[65] In the authors' experience, several antibodies are not sensitively detected by tissue-based assays (eg LGI1, glycine receptor, CASPR2, glycine receptor, AQP4, and MOG), but they are detected sensitively and specifically using the antigen-transfected cell-based assay format.[14,66-68] Seronegativity does not rule out an autoimmune diagnosis.

Certain antibodies require interpretation in the clinical context. For example, P/Q-type calcium-channel antibodies (always tested for using radioimmunoprecipitation assay in serum) may be informative for a diagnosis of Lambert-Eaton myasthenic syndrome or autoimmune cerebellar ataxia, but when detected outside of that context they are more commonly false positives.[69] Other neural antibodies need to be interpreted based on antibody titer. For example, GAD65 antibody is detected in 5% to 8% of the general population, particularly among patients with type 1 diabetes, pernicious anemia, or autoimmune thyroid disease, but it is generally only supportive of GAD65 neurological autoimmunity (eg, stiff person syndrome, ataxia, epilepsy) at values greater than 10,000 IU by ELISA (greater than 20 nmol/L by immunoprecipitation assay).[3] Non-neural antibodies, such as thyroid antibodies, have limited utility because they are commonly positive in the general population or those with non-neurologic autoimmune disease, as exemplified by **CASE 1-3**.[70] For example, a patient with autoimmune encephalitis who is seronegative may still meet criteria for definite limbic encephalitis. To further enhance diagnostic sensitivity, serum and CSF samples from patients who are seronegative can be evaluated in a laboratory with expertise in research antibody testing.

KEY POINT

- **Antibody testing in patients with autoimmune neurologic disease should be based on the phenotypic presentation. Given the growth in antibody biomarkers and the complexity of testing, the authors recommend using profiles designed by neuroimmunologist experts.**

Cancer Screening

For suspected paraneoplastic disorders, in the setting of antibody positivity with strong cancer association, testing may be quite narrow, such as fluorodeoxyglucose PET-CT (orbits to thighs) to identify small cell carcinoma in a patient with ANNA-1 (**TABLE 1-1** and **TABLE 1-2**).[71] In other patients in whom the antibody has more diverse cancer associations, a broader evaluation might be required, such as a search for both breast cancer and lung cancer in a woman with amphiphysin autoimmunity. In seronegative patients in whom paraneoplastic causation is suspected, or in those with an antibody with lower prediction for cancer, comprehensive testing for cancer could be undertaken. The repertoire of tests could include CT imaging of chest, abdomen, and pelvis, supplemented, as appropriate, by CT of the neck, gastrointestinal endoscopic studies, MRI or ultrasonography of the gynecologic tract, scrotal ultrasonography, pelvic MRI, or mammography. Whole-body PET-CT is sensitive for carcinoma or lymphoma in primary screening instead of CT, or after initially normal CT. High-resolution CT or MRI of the chest is preferred for detecting thymoma. Surgical exploration may be appropriate in select patients. For example, patients who are positive for Ma2 antibodies and ultrasound-detected testicular microcalcifications could lead to orchiectomy, given these findings have a strong link with testicular cancer. For patients with a high-risk paraneoplastic antibody and compatible neurologic syndrome

(or for those with intermediate-risk antibodies and high-risk phenotype) in whom initial cancer screening is negative, repeat screening should occur every 6 months for 2 years.[4] For patients with low-risk antibodies who are seronegative, cancer screening at the time of neurologic diagnosis is generally deemed sufficient, with age- and sex-appropriate cancer screening occurring thereafter.

TREATMENT, PROGNOSIS, AND RATING SCALES

In general, for most autoimmune neurologic disorders, treatment is based on Class IV evidence (eg, retrospective clinical data or expert opinion) (TABLE 1-1 and TABLE 1-2). However, some clinical trials, including phase 3 trials have been accomplished and demonstrated efficacy. Examples include eculizumab in patients with myasthenia gravis and AQP4 antibody–positive NMOSD and inebilizumab, ravulizumab, rituximab, and satralizumab in patients with NMOSD.[72-77] Efficacy for intravenous immunoglobulin (IVIg) has been demonstrated in phase 3 trials for stiff person syndrome, AIDP, CIDP, myasthenia gravis, and autoimmune epilepsy.[78-80] Some general principles include (1) initiating treatment in suspected cases once reasonable diagnostic alternatives have been excluded (ie, treat before the antibody test results become available), (2) observing responses for objective improvements (eg, for cognitive complaints use standardized neuropsychometric testing; for ataxia use video, wearable technology, or motion analysis; for dysautonomia use thermoregulatory sweat test, autonomic reflex testing, or gastrointestinal transit studies), (3) sustaining treatment over time because 5 days of treatment are unlikely to bring about sustained remission, and (4) considering maintenance therapy especially if the risk of relapse is high.[81] The authors typically use the following protocol that incorporates short-term and long-term therapeutic phases:[82]

- **Maximum reversibility (determined by comparison of objective baseline testing of main deficits compared with postimmunotherapy testing), also called the diagnostic test. It involves 4 to 8 weeks of IV methylprednisolone or IVIg or high-dose oral prednisone**
- **Maintenance of reversibility using long-term immunotherapy in chronic autoimmune diseases**
- **Minimal therapeutic dosage to reduce the side effect profile**

Short-term therapies are designed to minimize injury and accelerate recovery, whereas more long-term therapies are focused on maintaining remission and preventing relapse.

Maintenance steroid-sparing therapies include a broad range of options such as bone marrow suppressants (eg, azathioprine, mycophenolate mofetil, cyclophosphamide) and B-cell therapies (eg, rituximab). Other novel immune targets are providing additional options for therapy, especially when standard therapies are unsuccessful (FIGURE 1-1 and FIGURE 1-2). These include IL-6 receptor–targeted therapies (eg, tocilizumab, satralizumab[83,84]), CD19-targeted therapies (eg, inebilizumab, chimeric antigen receptor T-cell therapy), proteasome inhibitor–targeting plasma cells (eg, bortezomib), and reduction of antibody production (eg, FcRn monoclonal antibodies [efgartigimod, rozanolixizumab[85,86]]). Prognosis varies but appears to be better in those treated earlier and, in some antibody-mediated disorders, such

as LGI1 encephalitis and Lambert-Eaton syndrome, more than T cell–mediated paraneoplastic disorders such as PCA-1 (FIGURE 1-1 and FIGURE 1-2).[14,87,88] Specialized rating scales to document disease severity (such as the Clinical Assessment Scale in Autoimmune Encephalitis score in autoimmune encephalitis and the Scale for the Assessment and Rating of Ataxia score in autoimmune ataxia) and to determine likelihood of immunotherapy response (such as the Response to Immunotherapy in Epilepsy and Response to Immunotherapy in Epilepsy and Encephalopathy scores in autoimmune epilepsy and autoimmune encephalitis) may be useful in the clinical setting and future clinical trials.[48,89,90]

KEY POINT

● Cancer testing in patients with autoimmune neurologic disease can be directed by specific antibody findings to just one modality (eg, positron emission tomography [PET]-CT in a patient who is positive for anti-Hu antibodies) or could be broader in patients with a suspicion for a paraneoplastic disorder without a high-risk antibody.

FUTURE DIRECTIONS

Neural antibody discovery, driven by significant technologic advances, remains a major driver in defining specific molecularly defined autoimmune neurologic disorders. The availability of high-throughput testing platforms allows for detailed immunophenotyping of both seropositive and seronegative diseases. This research will provide immunologic multiomic insights by defining immunoglobulin targets and subclasses (eg, single-cell immunophenotyping in CSF and blood as well as lymph nodes), cytokine and chemokine profiles, disease-specific polyclonal immunome signatures (eg, phage display approaches), neural injury and other inflammatory (eg, complement proteins) biomarkers, and immunopathogenic insights from biopsy and autopsied tissues. These insights will provide an improved understanding of the immunopathogenic mechanisms involved in the initiation and persistence of the immunologically driven injury and provide targets for the repurposing of available therapies or provide novel targets for new drug discovery. Personalized precision-medicine approaches for these disabling conditions will provide hope for patients in the future.

With increasing complexity comes challenges for access to new diagnostic tests, particularly in the face of resource limitations or in countries without access to specialized testing laboratories. Obtaining serum from dried blood spots, which can be mailed internationally without the need for phlebotomy kits, is feasible, and early studies have shown promising comparability to standard serum draws for AQP4 IgG testing.[91] The major advances in the NMOSD arena with three US Food and Drug Administration (FDA) approved drugs in the past 4 years have paved the way for new trials in other antibody-defined disorders. The current partnership with pharmaceutical companies in phase 2/3 trials in MOGAD and autoimmune encephalitis trials is encouraging. A critical goal for autoimmune neurology is to advance treatment options for patients with paraneoplastic and idiopathic cytotoxic T cell–mediated diseases. No meaningful therapeutic advance has been made in this arena for 50 years. Future directions will include stem cell transplantation, tolerization, chimeric antigen receptor T-cell therapies, targeting pathogenic T cells, and T cell–specific drugs and monoclonal antibodies.

CONCLUSION

Autoimmune neurology has become a mainstream subspecialty that intersects with all traditional neurologic disciplines. Autoimmunity should be considered in patients with various persistent neurologic symptoms of subacute onset.

Evaluation is enhanced by careful clinical and paraclinical documentation of the phenotype; consideration of metabolic, infectious, oncologic, and other inflammatory diagnoses; and phenotype-specific autoimmune evaluations of serum and CSF, as appropriate. Immunotherapy should be initiated in patients after reasonable exclusion of non–immune-mediated diagnoses while autoimmune laboratory tests are pending. Antibody test results can further refine cancer workup, immunotherapy choices, and prognosis. Randomized controlled trials have led to approved therapies in myasthenia gravis and NMOSD and are underway for autoimmune encephalitis.

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DISCLOSURE

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serving as a consultant for Arialys Therapeutics, F. Hoffman-LaRoche Ltd, Genentech, Inc, Prime Therapeutics LLC, Sage Therapeutics, Inc, and UCB S.A., and on a scientific advisory or data safety monitoring board for F. Hofman-LaRoche Ltd, Genentech, Inc, and UCB S.A.; in the range of $5000 to $9999 for serving on a scientific advisory or data safety monitoring board for F. Hoffman-LaRoche Ltd; and intellectual property interests from a discovery or technology relating to health care. The institution of Dr Pittock has received personal compensation in the range of $500 to $4999 for serving as a consultant for Alexion Pharmaceuticals, Inc, Astellas Pharma Inc, Genentech, Inc, and Horizon Therapeutics plc; in the range of $5000 to $9999 for serving on a scientific advisory or data safety monitoring board for Alexion Pharmaceuticals, Inc; and research support from Alexion Pharmaceuticals, Inc, AstraZeneca, Genentech, Inc, Grifols, S.A., Horizon Therapeutics plc, the NIH, and NovelMed Inc.